Intronic polyadenylation of PDGFRalpha in resident stem cells attenuates muscle fibrosis.

Journal: Nature

Publication Year: 2016

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PubMed link: 27894125

Funding Grants: Molecular regulation of stem cell potency

Public Summary:
Platelet-derived growth factor receptor α (PDGFRα) is a protein that is anchored on the cell surface. This protein exhibits divergent effects in skeletal muscle. At physiological levels, signalling through this protein promotes muscle development in growing embryos and the formation of new blood vessels in injured muscle undergoing regeneration in adult animals. However, abnormally high activity of this protein often found in aged or diseased muscle causes the accumulation of scar tissues following muscle injury, which interferes with muscle function and limits the effectiveness of gene- and cell-based therapies for muscle disorders. Although compelling evidence exists for the role of this protein in scar tissue formation, little is known about the cells through which this pathway acts. Here we show in mice that signaling through this protein regulates a population of skeletal muscle resident cells that play a supportive role in muscle repair but may also cause scar tissue accumulation when aberrantly regulated. We found that these cells possess different ways to process PDGFRα protein to generate long and short variants. The short variant acts to prevent the over-activation of this protein and pathway and thus inhibit scar tissue formation. These findings provide novel mechanisms for potential therapeutic intervention of scar tissue accumulation following muscle injury or during aging.

Scientific Abstract:
Platelet-derived growth factor receptor alpha (PDGFRalpha) exhibits divergent effects in skeletal muscle. At physiological levels, signalling through this receptor promotes muscle development in growing embryos and angiogenesis in regenerating adult muscle. However, both increased PDGF ligand abundance and enhanced PDGFRalpha pathway activity cause pathological fibrosis. This excessive collagen deposition, which is seen in aged and diseased muscle, interferes with muscle function and limits the effectiveness of gene- and cell-based therapies for muscle disorders. Although compelling evidence exists for the role of PDGFRalpha in fibrosis, little is known about the cells through which this pathway acts. Here we show in mice that PDGFRalpha signalling regulates a population of muscle-resident fibro/adipogenic progenitors (FAPs) that play a supportive role in muscle regeneration but may also cause fibrosis when aberrantly regulated. We found that FAPs produce multiple transcriptional variants of Pdgfra with different polyadenylation sites, including an intronic variant that codes for a protein isoform containing a truncated kinase domain. This variant, upregulated during regeneration, acts as a decoy to inhibit PDGF signalling and to prevent FAP over-activation. Moreover, increasing the expression of this isoform limits fibrosis in vivo in mice, suggesting both biological relevance and therapeutic potential of modulating polyadenylation patterns in stem-cell populations.